

# RESEARCH

## in review

Volume 18 • Summer 2009

Research News from the San Francisco VA Medical Center  
and NCIRE — The Veterans Health Research Institute

## Featured PI

### Daniel H. Mathalon, MD, PhD

Daniel H. Mathalon, MD, PhD, is working to create a more accurate method of predicting who will develop schizophrenia, a psychosis he characterizes as “a lifetime illness that deprives people of some of the essential functions that make us human, that make us social beings.”

The SFVAMC staff physician focuses on the prodromal phase of the illness, when individuals are beginning to show signs and symptoms that indicate future risk. “Only about 30 percent of these high-risk individuals actually go on to develop schizophrenia, which means that 70 percent do not – and we don’t want to treat people who don’t need treatment,” says Dr. Mathalon, who is also an Associate Professor of Psychiatry at UCSF.

In the hope of identifying future schizophrenia patients more accurately, Dr. Mathalon is investigating whether people in the prodromal stages display the same kinds of brain abnormalities that are known to exist in people with the full-blown illness. To do that, he and his colleagues are measuring brain functions such as memory and attention during the performance of various tasks, using functional magnetic resonance imaging and a type of EEG measurement known as event-related potentials.

So far, he and his colleagues are seeing EEG results indicating that at-risk individuals

who exhibit the same brain abnormalities as full-blown schizophrenia patients convert to the disease at a higher rate than individuals who do not. “So we’re cautiously optimistic,” he says. “If we can accurately predict the course of the disease in the majority of cases, we will feel more confident about pursuing treatments at the early phase of illness, knowing that we will actually be able to help prevent the onset, or to at least delay it and reduce its severity, in a preponderance of the people that we treat.”

Treatment itself is another story, cautions Dr. Mathalon: “Fundamentally, we haven’t changed the way we treat schizophrenia since the introduction of Thorazine in the early 1950s.” He explains that Thorazine and related medications work by blocking receptors in the brain for the neurotransmitter dopamine, which has been implicated in schizophrenia and other psychoses. “The problem is that this approach is effective for maybe only about one third of patients, and partially effective for maybe another third,” he says. “Fortunately, there are new drugs on the horizon, targeting the neurotransmitter glutamate, that show antipsychotic benefits. So we’re hopeful that we may have the beginnings of alternative drug treatments for patients who don’t respond to the dopamine blocking agents. Or we might find that there are benefits in targeting multiple neurotransmitter systems in the brain.”



*Dr. Mathalon and SFVAMC schizophrenia researcher Judith Ford, PhD, are married and have a son, Adam. Dr. Mathalon also likes “cooking, music, and city life in San Francisco.”*

In other research, Dr. Mathalon is collaborating with Professor Sophia Vinogradov, MD, SFVAMC Associate Chief of Mental Health for Research and Education, who is using a therapeutic technique called cognitive remediation to improve attention and memory processes in schizophrenic patients. “It turns out that in patients with schizophrenia, deficits in attention and memory seem to be the most important factor in determining how they do in life, much more than if they have hallucinations or delusions,” says Dr. Mathalon. “Sophia and I are using EEG and MRI to measure what is changing in the brains of patients who are responding to this treatment. Can we document that there is normalization of function for some of the biomarkers we study?”

Dr. Mathalon emphasizes that “if we’re going to make a difference in this illness, we have to identify and ultimately treat people early, before the psychosis really becomes entrenched. So that’s the context of my work: we need more than just clinical symptoms to use in identifying who’s at risk.”

## Who is the VA/NCIRE Research Community?

Our research community at SFVAMC is a mixture of VA, NCIRE, and UCSF investigators. In most cases, researchers are associated with all three institutions, giving our community a broad and stable infrastructure. In this publication, we hope to introduce you to our brightest stars and the many interesting areas of research that are carried out here on our campus.



SFVAMC staff physician Beth Cohen, MD, studies the effects of post-traumatic stress disorder on physical health, particularly heart health. Dr. Cohen, who is also an Assistant Professor of Medicine at UCSF, observes that there is a well-known connection between PTSD and an increased risk of developing and dying from cardiovascular disease. “But there are a number of unanswered questions,” she says. “One is, what’s going to happen now with our current generation of veterans? Another is, why does PTSD increase the risk for heart disease to begin with?”

To answer the first question, Dr. Cohen has been working with Karen Seal, MD, MPH, founder and Co-director of the SFVAMC OEF/OIF Integrated Care Clinic, to look at cardiac risk factors in VA patients who have come back from Iraq and Afghanistan. “What we found,” she reports, “is that if you divide the veterans into those who have no mental health issues and those who do, the ones with a mental health diagnosis have much higher rates of a number of cardiovascular risk factors,” including smoking, obesity, diabetes, hypertension, and high cholesterol. “This goes along with what we’re seeing in the OIF/OEF Integrated Clinic,” says Dr. Cohen. “A lot of younger veterans who are struggling with adjustment and mental health issues describe

taking up smoking or using alcohol to sort of calm their nerves and self-treat their symptoms. Some say that they used to be very physically active but since they’ve been back, they’ve had low motivation or they have injuries, so they’re not exercising and they’ve gained a lot of weight. So they’re at risk for further problems down the line.”

To explore the potential underlying connection between PTSD and heart disease, Dr. Cohen is working with her primary mentor, SFVAMC staff physician and UCSF Professor of Medicine Mary Whooley, MD. “The main project is the Mind Your Heart study,” says Dr. Cohen. “We’re recruiting veterans from any war, both with and without PTSD. We’ll evaluate their heart health at the beginning and then follow them over time to see the differences between the two groups – and then try to figure out the links.”

Dr. Cohen believes the PTSD-heart health connection is based on a combination of factors. “For people who are struggling with mental health issues, it may be harder to keep a healthy diet and exercise regularly. They may smoke or drink more, as well,” she notes. “But I think there’s also a biological effect of PTSD.” She points out that hyperarousal – constant activation of the “fight-or-flight”



Dr. Cohen loves cooking, “particularly baking – although since I’m doing all this work on heart disease, I have to limit myself! I do fitness-based dance, and yoga, which helps me deal with stress. I love to be outdoors, and hike and snowboard when I can.”

sympathetic nervous system – is a common symptom of PTSD. “This can have direct and damaging effects on the heart.”

Dr. Cohen’s hope is that by identifying the key factors that link PTSD with increased heart disease risk, “we can then intervene and hopefully reduce risk of further heart events in people who have already developed heart disease, but also prevent heart disease in the younger generation of veterans who haven’t yet developed it. It will be interesting to see,” she concludes, “if treating PTSD also improves

## SFVAMC Honored by Secretary of Veterans Affairs Visit



VA Secretary Eric Shinseki and members of the VA community.

icine research from Lt. Col. Sloane Guy, MD, who spoke live from Iraq via video teleconference.

Secretary Shinseki also heard briefings from SFVAMC researchers Karen Seal, MD, MPH, Michael Weiner, MD, Thomas Neylan, MD, Raymond Swanson, MD, William Marks, MD, and Gerald Matson, PhD.

Secretary of Veterans Affairs Eric K. Shinseki visited SFVAMC on June 29, 2009. After being welcomed by Medical Center Director Lawrence H. Carroll, Secretary Shinseki heard presentations on various aspects of research and clinical care at SFVAMC.

The Secretary heard research overviews from Lynn Pulliam, MS, PhD, and NCIRE Executive Director Robert E. Obana, and received a briefing on telemed-

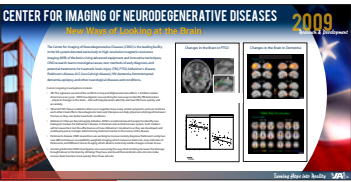
## National Research Week 2009 Celebrated at SFVAMC

“Turning Hope Into Reality” was the theme as SFVAMC celebrated VA Research Week in May, 2009.

As part of a nationwide observance in honor of VA research, there were public lectures from selected SFVAMC investigators on a variety of topics: Gary Abams, MD, Peter Elias, MD, Rebecca Sudore, MD, Mary Whooley, MD, and Sei Lee, MD.

In addition, there were educational posters designed by NCIRE Design and Creative Services Manager Sue Dugdale on display throughout the Medical Center.

SFVAMC has the largest medical research program in the VA system, with field-leading research centers in cancer, cardiovascular disease, dermatology, geriatrics and patient care, HIV/AIDS, infectious disease, mental health, musculoskeletal disease, nephrology, neuroimaging, and neurosciences.



Research posters were displayed throughout the SFVAMC.

# The Brain at War

## NCIRE Sponsors 2<sup>nd</sup> Annual Brain at War Conference



The second annual gathering of The Brain at War conference met at SFVAMC on Thursday, May 28. The event, sponsored by NCIRE, brought together some of the world’s leading experts on post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), and related neurological and psychological conditions.

The proceedings opened with remarks by SFVAMC Director Lawrence H. Carroll, who welcomed the participants and expressed appreciation and support for “the vitally important work being done by those attending this conference.”



Col. Karl E. Friedl of TATRC, Dr. Lynn Pulliam, and Dr. Michael Selzer of the Department of Veterans Affairs (L to R)

Presenters and guests included Brigadier General Loree K. Sutton, MD, Director of the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury; Michael E. Selzer, MD, PhD, Director of Rehabilitation Research and Development at the Department of Veterans Affairs; and Colonel Karl Friedl, PhD, Director of the US Army’s Telemedicine and Advanced Technology Research Center (TATRC), which funds much of NCIRE’s military-related neuropsychological research.

Brig. Gen. Sutton spoke about the Real Warriors campaign, an initiative launched by the Defense Center of Excellence to build resilience, facilitate recovery, and support reintegration of returning service members, veterans, and their families.

Speaker of the House Nancy Pelosi (D-Calif.) said in a letter to conference participants, “It is a privilege to support NCIRE and The Brain at War conference. It is essential that we lift the unwarranted stigma associated with PTSD and TBI and work vigorously to offer the best available treatment to all our veterans.”



Lt. Col. Sloane Guy, MD, listens from Iraq as NCIRE Executive Director Robert E. Obana addresses the conference

The highlight of the day was a research presentation on “Advances in Telesurgery and Telementoring” by US Army surgeon Lieutenant Colonel T. Sloane Guy, MD, who spoke via video teleconference from the 47th Combat Support Hospital in Iraq, where he is Chief of Surgery. Dr. Guy did the initial research on his project while serving in his previous posting as a cardiothoracic surgeon at SFVAMC.

“Dr. Guy’s story exemplifies the kind of multi-institutional scientific initiative that NCIRE works to foster,” said NCIRE Executive Director Robert E. Obana. “It’s hard to describe how exciting this was for everyone at the conference.”

Other presenters included Charles Marmar, MD, SFVAMC Chief of Mental Health and UCSF Professor and Vice Chair of Psychiatry; Raymond Swanson, MD, SFVAMC Chief of Neurology and Rehabilitation and UCSF Professor and Vice Chair of Neurology; and Karen Seal, MD, MPH, founder and Co-Director of the OEF/OIF Integrated Care Clinic at SFVAMC and UCSF Assistant Professor of Medicine.



Brigadier General Loree Sutton, MD, Director of the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury, speaks with SFVAMC neurosurgeon Grant Gauger, MD

## The Veterans Health Research Institute

### News

by Robert Obana, Executive Director

One of the high points of this year has been “The Brain at War” conference held in May, which in just two years has become one of the premier conferences on PTSD, traumatic brain injury, and related neuropsychological consequences of war. NCIRE was delighted to welcome some of the leading experts in these fields from the Department of Defense, the uniformed services, the VA, and academia. “The Brain at War” also received enthusiastic support from our Congressional supporters: Senators Dianne Feinstein and Barbara Boxer and Speaker of the House Nancy Pelosi, who said in a letter to the gathering, “It is a privilege to support NCIRE and “The Brain at War conference.”

The recent visit of Veterans Affairs Secretary Eric K. Shinseki was very inspiring, given his noted interest in veterans health research and considering NCIRE’s model of collaboration as a means to help transform the VA to meet the emerging health needs of veterans.

On the research front, I am very pleased to note that after years of flat budgets, the National Institutes of Health has received a sizable amount of federal stimulus funds set aside specifically for research. Our investigators have responded quickly and enthusiastically to the opportunity to obtain some of these funds for their research projects, and we have every hope that a number of their proposals will be approved. In terms of continued research funding, we can most likely look forward to further increases in the NIH budget for fiscal 2010; however, beyond that, the picture is cloudy and depends to a large extent on the overall performance of the US economy.

As many of you are aware, NCIRE has embarked on a program to develop and expand our Board of Directors in order to create a more active culture of philanthropy. These efforts have already made an impact for NCIRE. Our new Board members – Rear Admiral John W. Bitoff, US Navy (Ret.), Brigadier General Andrew P. Grose, US Air Force (Ret.), and Major General J. Michael Myatt, US Marine Corps (Ret). – have added real value, as has our new Board Advisor, John Kerner, MD, US Army Medical Corps (Ret.). We thank them all and look forward to their continued energy, commitment, and positive contributions.



## Lynn Pulliam, MS, PhD, Honored by NeuroVirology Society



Lynn Pulliam, MS, PhD

Lynn Pulliam, MS, PhD, Chief of Microbiology and former ACOS of Research & Development at SFVAMC, has received two significant honors from the International Society for NeuroVirology (ISNV).

Dr. Pulliam was selected to present the Society's 2009 Women in Neuroscience Lecture. The lectureship was established to emphasize and celebrate the major contributions of outstanding women in the advancement of biomedical science, and in particular neurovirology and related disciplines. Dr. Pulliam was recognized for her groundbreaking work on mechanisms of neuroinflammation, HIV infection in the brain, and HIV dementia.

In addition, Dr. Pulliam, who is also a Professor of Laboratory Medicine and Medicine at UCSF, was elected President of the ISNV for 3 years beginning in January 2010.

## Grants Funded

December 2008 – June 2009

### American Heart Association – National

#### Jialing Liu, PhD

The Recovery of Post Stroke Mild Cognitive Impairment: An Experimental Model  
01/01/09 – 12/31/14

### Department of the Army

#### Lynn Pulliam, MS, PhD

Traumatic Brain Injury Impacts  
03/01/09 – 02/28/11

#### Midori Yenari, MD

Regulation of Matrix Metalloproteinases by Heat Shock Protein and Brain Injury  
05/01/09 – 04/30/10

### Department of Defense

#### Charles Marmar, MD

Biomarkers for PTSD – 06/03/09 – 06/02/10

#### Charles Marmar, MD

Online PTSD Diagnosis and Treatment Training for Primary Care Physicians  
02/16/09 – 03/15/10

### Melanoma Treatment Alliance

#### Maria Wei, MD

Sphingosine 1-Phosphate and Cardioprotection – 06/01/09 – 05/31/11

### National Institutes of Health (NIH)

#### Joel Karliner, MD

Sphingosine 1-Phosphate and Cardioprotection – 03/16/09 – 02/28/14

#### Lynn Pulliam, MS, PhD

Hepatitis C Drives Neuropathogenesis in HIV/HCV Coinfection Patients  
06/05/09 – 04/30/12

#### Paul Sullam, PhD

Role of Streptococcal-Platelet Binding in Endocarditis – 12/01/08 – 11/30/13

#### Michael Weiner, MD

Prediction of Cognitive Decline with MRI and MRS – 03/15/09 – 02/28/14

### National Space Biomedical Research Institute

#### Nick Kanas, MD

Crew Interactions and Autonomy During Long Duration Isolation and Confinement  
03/01/09 – 02/28/10

### University of Maryland

#### David Lovett, MD

Mechanisms of MMP-2 Transcription in Hindlimb Ischemia – 05/01/09 – 04/30/10

#### Joseph Rapp, MD

Fibrotic Effects and Resolution of MMP Proteins in Thrombus Resolution  
05/01/09 – 04/30/10

### VA Career Development Award

#### Karunesh Ganguly, MD, PhD

A Brain-Machine Interface Using the Ipsilateral Arm Representation  
08/01/09 – 07/31/14

#### Neil Trivedi, MD

A Genomic, Proteomic and Clinical Analysis of Human Mast Cell Tryptases  
07/01/09 – 6/30/14

#### Meshell Johnson, MD

Sodium and Chloride Transport in Alveolar Type I Cells  
07/01/09 – 06/30/14

### VA Research & Development REAP

#### Raymond Swanson, MD

Multimodal Strategies for Improving Recovery from Brain Injury  
07/01/09 – 06/30/14

### VA Merit Review BLR&D

#### Daniel Lim, MD

Role of MLL Chromatin Remodeling Factor in Neural Stem Cells  
07/01/09 – 06/30/12

## RESEARCH in review

### A SFVAMC/NCIRE Publication

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